psychCME TV Learning Objectives

II. Utilize evidence-based judgement to assess the tolerability profile of different treatments in the CATIE trial

psychCME TV Learning Objectives

III. Recognize the clinical merit of trials that include participants who reflect a wide range of disease states and phenomenology

Aims of CATIE

- To determine how second-generation antipsychotic drugs compare to first-generation antipsychotic drugs
- To determine how second-generation antipsychotic drugs compare to each other
- To determine if second-generation antipsychotic drugs are cost-effective

Lieberman JA, et al. *N Engl J Med* 2005 Sep 22;353(12):1209-23.

Clinical Trials in Schizophrenia
Limitations of Our Knowledge

Published studies have significant limitations:

- Predominantly short-term studies designed for regulatory approval and labeling language
- Comparators are either placebo or a single active agent
- Results have limited generalizability because they lack representative patient samples, clinical settings, and treatment conditions
- Sponsored by pharmaceutical companies
- Clinical experience and case reports are not an adequate substitute for data

CATIE Schizophrenia Trial
Overview

- Sponsored by NIMH
- Participants
  - 1460 people with schizophrenia
- Trial duration
  - Subjects participate for 18 months
- Design
  - Pragmatic trial that is a hybrid of efficacy and effectiveness trial designs

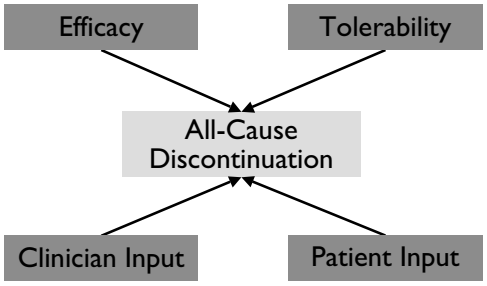
Lieberman JA, et al. *N Engl J Med* 2005 Sep 22;353(12):1209-23.

CATIE: Broad Inclusion and Minimal Exclusion Criteria

- DSM-IV schizophrenia, 18-65 years old
- Not first-episode or treatment-resistant
- Concomitant medications, medical illnesses, substance use disorders allowed
- Conducted at 57 geographically, demographically, and organizationally diverse sites

Lieberman JA, et al. *N Engl J Med* 2005 Sep 22;353(12):1209-23.

Primary Outcome Measure
All-Cause Treatment Discontinuation

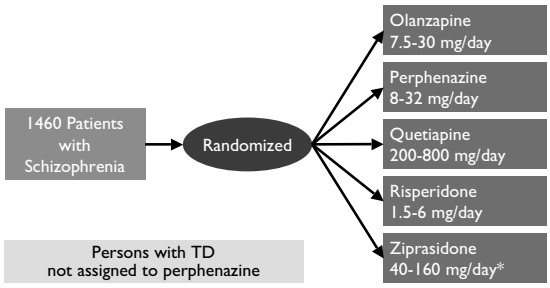


Lieberman JA, et al. *N Engl J Med* 2005 Sep 22;353(12):1209-23.

Secondary Outcomes

- Reasons for discontinuation:
  - Efficacy, tolerability, and patient decision
- Psychopathology
- Safety
- Service utilization and costs
- Neurocognition
- Treatment adherence
- Comorbidity
- Quality of life
- Substance use
- Violence

CATIE Phase I
Double-Blinded and Randomized



* Ziprasidone added after 40% sample enrolled

Lieberman JA, et al. *N Engl J Med* 2005 Sep 22;353(12):1209-23.

Demographic and Clinical Characteristics

Assessment	Total (N = 1460)
Demographics	
Age mean (SD)	40.6 (11.1)
Gender Male	1080 (74%)
Race - White - Black/African-American - All other race groups	874 (60%) 513 (35%) 71 (5%)
Spanish/Hispanic/Latino ethnicity	170 (12%)
Education (years)	12.1 (2.3)

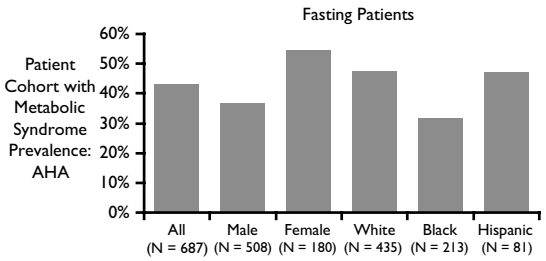
Lieberman JA, et al. *N Engl J Med* 2005 Sep 22;353(12):1209-23.

Demographic and Clinical Characteristics

Assessment	Total (N = 1460)
Demographics	
Marital Status - Married - Previously Married - Never Married	 167 (11%) 425 (29%) 868 (59%)
Unemployed	1217 (85%)
Exacerbation in Past 3 Months	402 (28%)
PANSS Total Score (30-210)	75.7 (17.6)
Clinician Rated CGI Severity Score (1-7) CG-S of 4 = "moderately ill"	4.0 (0.9)

Lieberman JA, et al. *N Engl J Med* 2005 Sep 22;353(12):1209-23.

Prevalence of Metabolic Syndrome in CATIE Trial Baseline Patients



- 40.9% of all patients met criteria for metabolic syndrome according to the ATP III definition

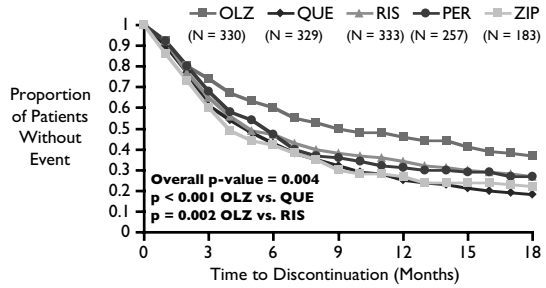
McEvoy JP, et al. *Schizophr Res* 2005 Aug 29.

CATIE Dosing mg/day

Drug	CATIE MEAN DOSE	Current Avg Dose in Schizophrenia	Study Range
ZIP	112.8	136.9	40-160
RIS	3.9	3.6	1.5-6.0
QUE	543.4	420.4	200-800
OLZ	20.1	15.7	7.5-30
PER	20.8		8-32

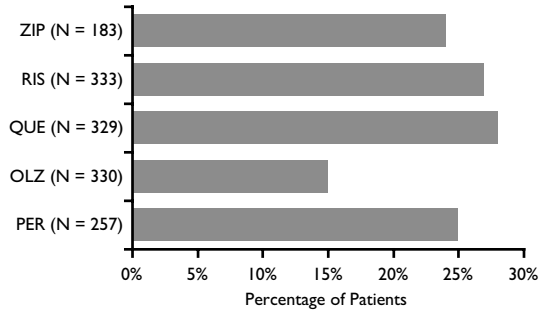
Lieberman JA, et al. *N Engl J Med* 2005 Sep 22;353(12):1209-23.
Average Dosing Data IMS, 9/05.

Time to Discontinuation for Any Reason



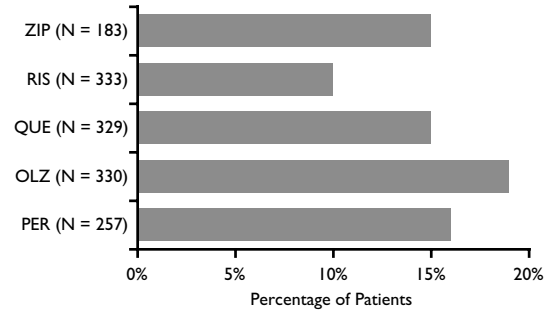
Lieberman JA, et al. *N Engl J Med* 2005 Sep 22;353(12):1209-23.

Treatment Discontinuation
Lack of Efficacy



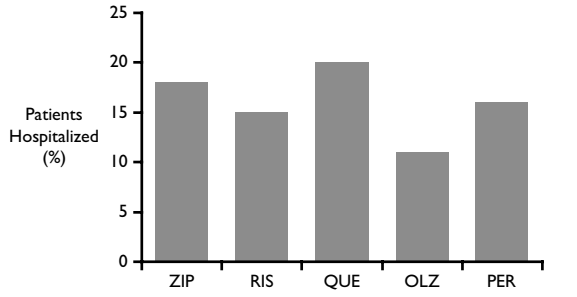
Lieberman JA, et al. *N Engl J Med* 2005 Sep 22;353(12):1209-23.

Treatment Discontinuation
Owing to Intolerability



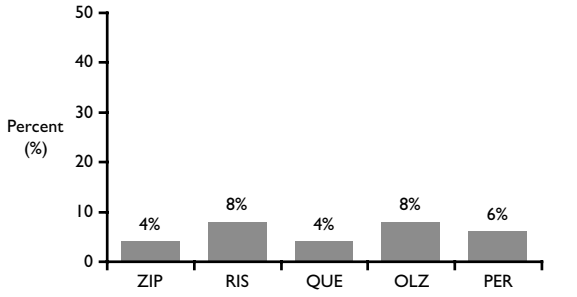
Lieberman JA, et al. *N Engl J Med* 2005 Sep 22;353(12):1209-23.

How Well Did Drugs Prevent Hospitalization?



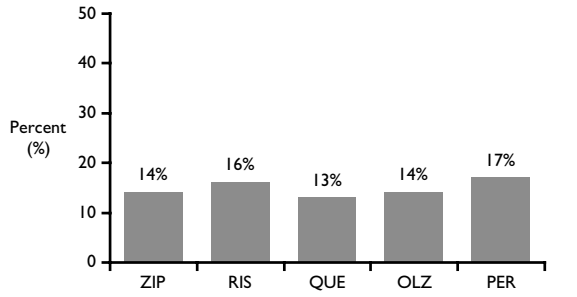
Lieberman JA, et al. *N Engl J Med* 2005 Sep 22;353(12):1209-23.

Simpson-Angus Extrapyramidal Signs Scale Mean Score ≥ 1



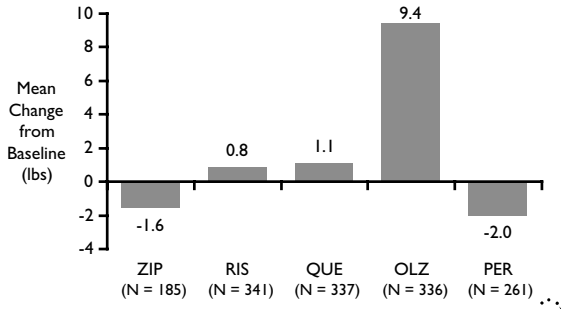
Lieberman JA, et al. *N Engl J Med* 2005 Sep 22;353(12):1209-23.

AIMS Global Severity Score ≥ 2



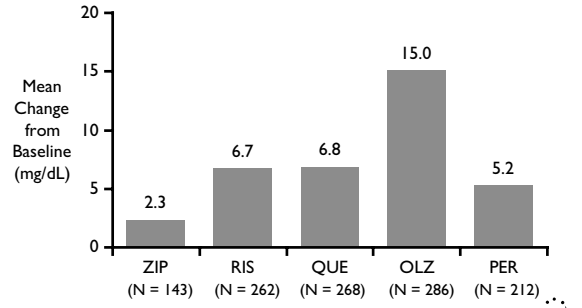
Lieberman JA, et al. *N Engl J Med* 2005 Sep 22;353(12):1209-23.

Weight Change



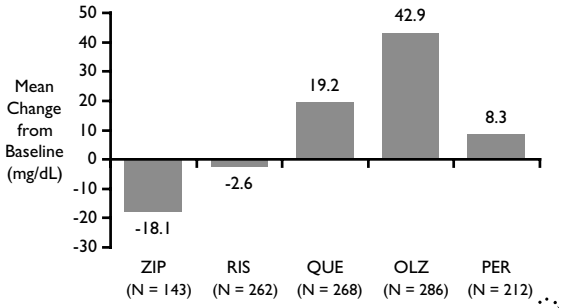
Lieberman JA, et al. *N Engl J Med* 2005 Sep 22;353(12):1209-23.

Glucose Levels



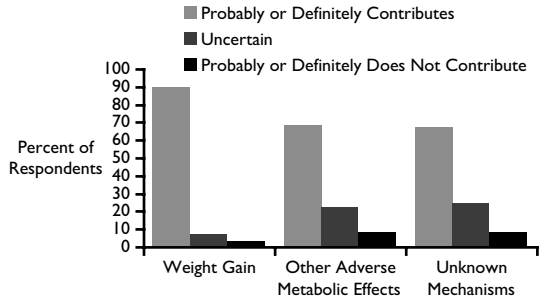
Lieberman JA, et al. *N Engl J Med* 2005 Sep 22;353(12):1209-23.

Triglycerides



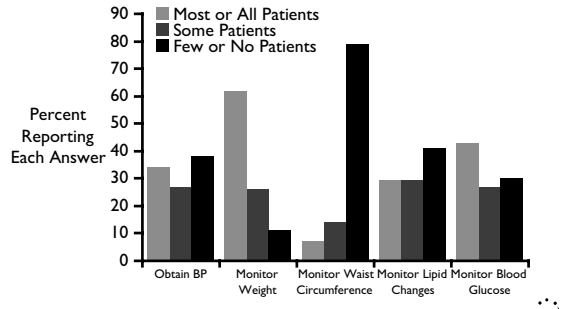
Lieberman JA, et al. *N Engl J Med* 2005 Sep 22;353(12):1209-23.

AtAMI: Contribution of Atypical Antipsychotics to Metabolic Issues



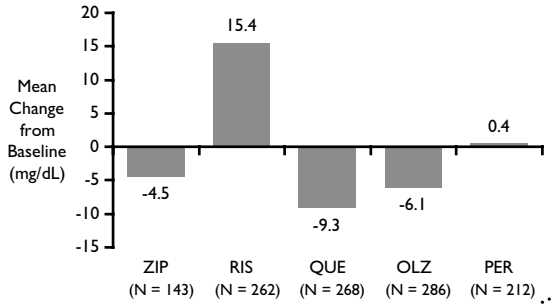
Newcomer JW, et al. *J Clin Psychopharmacol* 2004;24 (Suppl 1):S1-6.

AtAMI: Patient Monitoring for Metabolic Risks



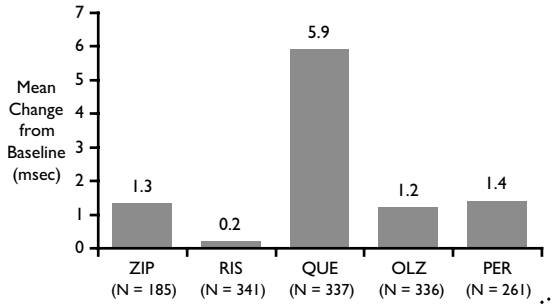
Newcomer JW, et al. *J Clin Psychopharmacol* 2004;24 (Suppl 1):S1-6.

Prolactin Levels



Newcomer JW, et al. *J Clin Psychopharmacol* 2004;24 (Suppl 1):S1-6.

Mean Change in QTc Interval



Lieberman JA, et al. *N Engl J Med* 2005 Sep 22;353(12):1209-23.

Concomitant Medications Added

Assessment	OLZ (N = 336)	QUE (N = 337)	RIS (N = 341)	PER (N = 261)	ZIP (N = 185)	p-value
Lithium	<1%	1%	<1%	1%	<1%	0.42
Anticonvulsants	3%	3%	4%	3%	4%	0.63
Antidepressants	12%	8%	16%	11%	14%	0.03
Hypnotics and Sedatives	7%	4%	9%	9%	9%	0.03
Anxiolytics	**9%**	**14%**	**10%**	**15%**	**15%**	**< 0.001**
Oral Glucose Lowering Drugs and Insulin	4%	2%	2%	2%	2%	0.95
Cholestatin Drugs	5%	4%	3%	3%	1%	0.28
Anticholinergic Agents	**8%**	**3%**	**9%**	**10%**	**8%**	**0.01**

Lieberman JA, et al. *N Engl J Med* 2005 Sep 22;353(12):1209-23.

The New York Times

Comparing Schizophrenia Drugs
Published: September 21, 2005

A government-financed study has provided the strongest evidence yet that the system for approving and promoting drugs is badly out of whack. The study compared five drugs used to treat schizophrenia and found that most of the newest, most heavily prescribed drugs were no better than an older drug that is far cheaper. The nation is wasting billions of dollars on heavily marketed drugs that have never proved themselves in head-to-head competition against cheaper competitors.

The whole class of antipsychotic drugs has had undeniable value in blunting the symptoms of schizophrenia, enabling many patients to leave mental hospitals and move into the community. But the first generation of these drugs fell into disfavor because they often caused neurological side effects, like tremors and other involuntary movements. That spurred the development of a new generation of drugs known as atypical antipsychotics, which now dominate the market and rake in some $10 billion in annual sales. The trouble is that these new drugs were approved largely on the basis of short-term clinical trials that compared them primarily with placebos, so there was little if any evidence that they were any better than many of the older drugs.

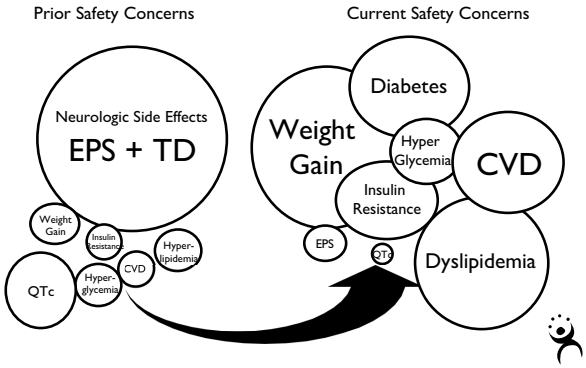
That gap has been filled by an 18-month clinical trial involving more than 1,400 adults around the nation. The study, sponsored by the National Institute of Mental Health, measured how long patients were able to keep taking their assigned drugs before deciding to change, usually because a drug wasn't working or had intolerable side effects. Three-fourths of the patients, a shocking number, stopped taking the drug they had been given, suggesting that there is a clear need for better treatments. The study found that the oldest drug, perphenazine, was as effective and caused no worse side effects than three of the newer drugs. Zyprexa, a new drug made by Eli Lilly, helped patients control symptoms slightly better than the others, but at the cost of serious side effects.

Doctors should find a trove of useful data in the study to help them decide which drug might be best for a particular patient. But Congress and the Bush administration ought to pay attention as well. Surely it would make sense to force manufacturers to test their drugs not just against placebos, but against existing drugs that they are seeking to displace. And surely it would be cost-effective for the government to sponsor large studies comparing a slew of expensive drugs with their cheaper alternatives.

NIMH Perspective on Reimbursement Based on CATIE

"We feel it is premature to alter reimbursement policies for the atypicals. A one size fits all policy for treating schizophrenia could be harmful, essentially turning the clock back 40 years. We hope that those making policy decisions about reimbursements will wait until the rest of the outcome data are available from this landmark study in order to inform more fully health care policy decisions for this highly vulnerable population."

Side Effects of Atypical Antipsychotics
Shift in Risk Perception



Clinical Pearls

- The NIMH-CATIE Study is the largest, longest, and most comprehensive independent trial comparing existing therapies for schizophrenia
- Treatment for persons with schizophrenia must be individualized
- Clinicians and patients must carefully evaluate the tradeoffs between efficacy and side effects when choosing agent
- Variance in efficacy and tolerability between drugs can be substantial for individual patients